A phase 1b/2, open-label, safety, tolerability and efficacy study of NC410 plus pembrolizumab for participants with immune checkpoint inhibitor (ICI) refractory or MSS/MSI-low ICI naïve advanced or metastatic solid tumors

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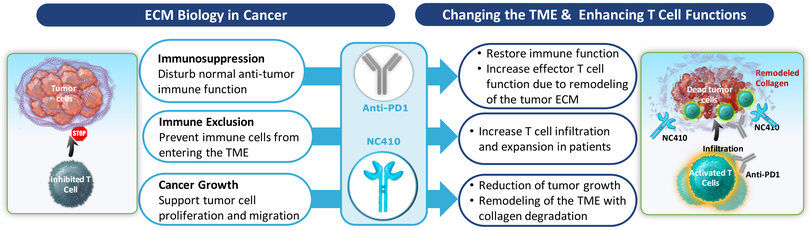
Abstract Number: 739

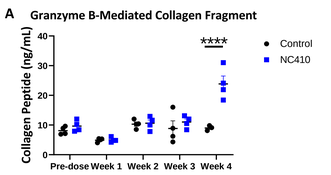
Background

Pembrolizumab (Keytruda®), a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) against programmed cell death 1 (PD1), has demonstrated significant activity in several tumor types, including microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC and dMMR non-CRC tumors. However, clinical benefit has been limited in many mismatch repair proficient (pMMR) tumors (DT Le 2015)[1], and a large subset of patients that initially respond, become refractory to treatment (RW Jenkins 2018)[2]. This lack of therapeutic activity is related to several factors, including an inhibitory Tumor Microenvironment (TME), reduced immunogenicity and activation of the TGF-β pathway, resulting in enhanced deposition of collagen in the tumor extracellular matrix (ECM). Enhanced collagen production in the ECM creates a physical barrier to immune cell infiltration and acts to directly inhibit immune cells by interacting with the inhibitory receptor, Leukocyte Associated Immunoglobulin-Like Receptor-1 (LAIR-1) on immune cells. Several recent publications on pre-clinical studies have demonstrated that this inhibition can be reversed by NC410, a recombinant form of the LAIR-2 protein, a naturally produced soluble decoy that normally functions to compete with LAIR-1 binding. NC410 is composed of LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1 (Ramos 2021)[3]. More recently, in vivo modeling studies demonstrated that treatment with PD(L)-1 blockade in a murine lung model drives enhanced collagen production due to an increase in TGF-β signaling, resulting in resistance to treatment targeting the PD-1 pathway. Genetically driven overexpression of LAIR-2, in this model was able to overcome resistance, sensitize tumors to PD(L)-1 blockade, reduce tumor growth, and increase local immune cell activation (Peng 2020)[4]. In addition, previous preclinical testing by NextCure and collaborators has demonstrated that the combination of NC410, and anti-PD(L)-1 leads to consistent reduction of tumor burden and enhanced survival in several animal models. Taken together, combination of NC410 with pembolizumab presents itself as a unique opportunity to enhance responses in patients with Immune Checkpoint Inhibitor (ICI) naïve microsatellite stable or microsatellite instability-low (MSS/MSI-L) tumors, and also, in patients who are refractory to ICI therapies. A clinical trial of NC410 Phase 1 monotherapy in participants with advanced or metastatic solid tumors is currently on-going. Preliminary clinical and biomarker data has been presented (Myint SITC 2021)[5] supporting immune activation and mechanism of action proposed for NC410.

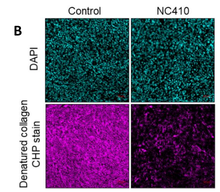
Rationale for Combination with NC410 and Pembrolizumab



Pre-Clinical Evidence of ECM Remodeling after NC410 Treatment



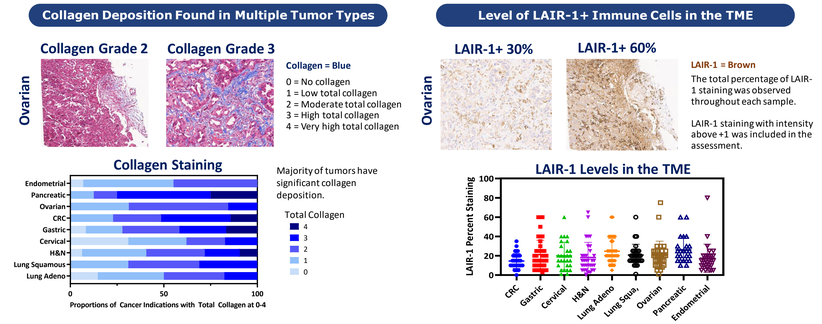
Ramos et al., *e-Life* 2021



Horn et al., *SITC* 2021[6] (with permission)

Figure **A**) Analysis of collagen degradation product C4G [type IV collagen degraded by granzyme B (T cell activity/infiltration)] in serum at baseline, at weeks 1, 2, 3 and 4. **B**) Representative images of DAPI (cyan, top) and the immunofluorescence-based staining of denatured collagen utilizing a collagen hybridizing peptide (CHP, magenta, bottom) in MC38 tumors. Mice were treated on day 9 and 11, and tumors were harvested on day 12.

Tumors Types with Enriched Collagen & LAIR-1



In Vivo Model: NC410 Synergizes with Anti-PD-L1 and Enhances Overall Efficacy

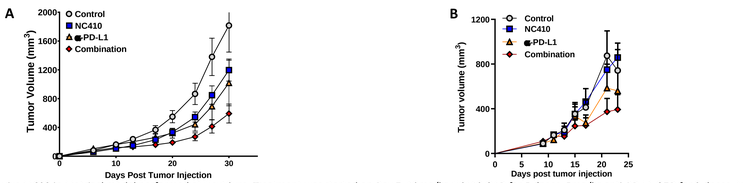


Figure **A**) *In vivo* MC38 in Matrigel model performed at NextCure. Treatment was started on Day 7. 10mg/kg NC410 Q4D for 5 doses; 5mg/kg anti-PD-L1 Q7D for 2 doses. N = 5 animals per group. **B**) *In vivo* MC38 in Matrigel model performed at Utrecht University. Treatment was started on Day 7. 10 mg/kg single dose or 5mg/kg in combination. Dosing bi-weekly. N = 14 animals per group.

NC410: Phase 1 Monotherapy Summary

SAFETY & TOLERABILITY	• NC410 is safe and tolerable.
	• Notable treatment related adverse events:
	  • Infusion Reaction: One Grade 3 at 200mg Q2W, Two Grade 2 at 100mg Q2W;
	  • Anemia: One Grade 3, Two Grade 2;
	  • Lymphopenia: One transient grade shift from Grade 2 at baseline to Grade 3.

CLINICAL BENEFIT	• Best response, stable disease: 8 stable disease > 12 weeks (22%) across different doses.

TARGET BINDING	• C1q: Transient reduction is early peripheral pharmacodynamic marker.
	  • Implies no long-term safety concern.
	• CDP (Collagen Derived Products):
	  • Trends in increased C4G (Granzyme B-mediated collagen fragment);
	  • Reduction in Pro-C3 and Pro-C6 (prognosis markers of tumor progression).

IMMUNE ACTIVATION	• CD4 and CD8: • Time-dependent increase without concomitant increase in LAIR-1 expression.
NC410 CLINICAL DEVELOPMENT PLAN	• Combination Therapies with Immune Checkpoint Inhibitors.

1. References:
1. Le DT et al., *N Engl J Med*. 2015;372:2509; 2. Jenkins et al., BJC. 2018;118;9-16; 3 Ramos MIP, Tian L, de Ruiter EJ, et al., *Elife*. 2021;10:e62927; 4. Peng et al., *Nature Communication* 2020, 11:4520; 5. Myint et al,. *SITC* 2021; 6. Horn et al., *SITC* 2021.

2. Acknowledgement: This study is in collaboration with MerckSharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

NC410 & Pembrolizumab Inclusion & Exclusion Criteria

Inclusion Criteria

- Be ≥ 18 years of age on day of signing informed consent.
- Participant with histologically or cytologically confirmed diagnosis of the following advanced unresectable and/or metastatic solid tumors:
  - Phase 1b: Participants with solid tumors regardless of prior treatment with ICIs or MSS/MSI status, including CRC, Gastric including GE junction, Esophageal, Ovarian, and H&N cancers.
  - Phase 2: ICI Refractory (Cohort 1):
    - CRC, Gastric including GE junction, Esophageal, Endometrial, and H&N cancer.
  - Phase 2: ICI naïve MSS/MSI-low (Cohorts 2a-2c):
    - CRC, Gastric including GE junction, and Ovarian cancers.
- Have measurable disease per RECIST 1.1.
- Able to provide tumor tissue at screening (fresh or archival).

Exclusion Criteria

- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137), and was discontinued from that treatment due to a Grade 3 or higher irAE.
- Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to treatment.
- Has received prior radiotherapy within 2 weeks of start of study treatment or has had a history of radiation pneumonitis.
- Has had an allogeneic tissue/stem cell/solid organ transplant.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
- Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

NC410 & Pembrolizumab Combo Study Design

Phase 1b

Advanced unresectable and/or metastatic solid tumors regardless of prior ICI treatment or MSS/MSI status, including:

CRC, Gastric including GE junction, Esophageal, Ovarian, and H&N

Pembrolizumab
400 mg Q6W
+
NC410 (escalating doses) Q2W

Endpoints:
- Safety and tolerability;
- Recommended Phase 2 dose of NC410 for combo.

Phase 2 Dose Expansion: Simon 2 Stage Design

ICI-REFRACTORY

Cohort 1
CRC, Gastric including GE junction, Esophageal, Endometrial and H&N

Pembrolizumab
400 mg Q6W
+
NC410 Combo RP2D Q2W

ICI-NAïVE

Cohort 2a
ICI naïve MSS or MSI –L CRC

Cohort 2b
ICI naïve MSS or MSI-L Gastric including GE junction

Cohort 2c
ICI naïve MSS or MSI-L Ovarian

Primary Endpoint
- Overall Response Rate (ORR) based on RECIST v1.1.

Secondary Endpoints
- Duration of Response (DoR), Progression Free Survival (PFS), Disease Control Rate (DCR);
- Overall Survival (OS);
- Safety;
- PK.

Exploratory Endpoints
- Tumor biopsy analyses including but not limited to:
  - Immune cell infiltrates, PD-L1 expression LAIR-1 and collagen staining, at baseline and following treatment.
- Blood sample analyses including but not limited to:
  - Immunophenotyping, cytokines & chemokines, C1q & CDP.